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Prevalence and Nutrition-Related Risk Factors of Hepatorenal Syndrome in Liver Cirrhosis Patients with Malnutrition

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KEYWORDS
Hepatorenal syndrome, cirrhosis, malnutrition, prevalence, risk factors.

ABSTRACT:

Objective: This study aimed to understand the prevalence of hepatorenal syndrome in malnourished patients with liver cirrhosis and identify nutrition-related risk factors associated with its development.

Methods: This retrospective study included 385 cirrhosis patients with signs of malnutrition admitted between January 2017 and December 2022. Patients were classified based on body mass index (BMI) and serum albumin level. HRS was diagnosed based on the International Ascites Club criteria (7, 8). Data on demographics, etiology, disease severity, laboratory parameters, and clinical outcomes were collected from medical records. Data were statistically analyzed for descriptive and multivariate parameters using SPSS software 23.0

Results:

The prevalence of HRS in the population with chronic malnutrition was 24.15%. HRS was significantly higher in severely malnourished patients with a BMI of 16.0 kg/m2 and albumin level of 2.8 g/dL (76.34%) than in mildly malnourished patients. A multivariate investigation revealed that a low body mass index (OR=2.5, 95% CI: 1.5-4.1) and low serum albumin (OR=3.2, 95% CI: 1.8-6.0) were independent risk factors for the development of HRS.

Conclusion: The study findings highlight the importance of nutritional support in the management of patients with cirrhosis to prevent the development of HRS. Further prospective studies are needed to validate our results and explore the potential mechanisms underlying the association between malnutrition and hepatorenal syndrome.

Introduction

Hepatorenal syndrome (HRS) is a serious complication of cirrhosis and is characterized by the development of acute kidney injury in patients with liver disease, with an estimated prevalence of 8-38% in patients with advanced liver disease. It is a potentially life-threatening condition, with a median survival of 6 months if left untreated [1]. The reported prevalence of HRS varies widely among different studies, ranging from 5% to 40% in patients with cirrhosis. A study conducted by Gines et al. in 2015 reported a prevalence of 18.7% in a large cohort of patients with cirrhosis [2].

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Another study by Arroyo et al. in 2016 reported a higher prevalence of 40% in patients with cirrhosis admitted to the hospital[3]. The risk factors identified for HRS are the severity of liver disease, bacterial infections, gastrointestinal bleeding, and the use of nephrotoxic drugs [4].

Malnutrition is a frequent finding in patients with cirrhosis, affecting up to 80% of individuals with advanced disease[5]. The presence of malnutrition has been associated with a higher risk of complications, such as infections, hepatic encephalopathy, and HRS, in patients with liver cirrhosis [6]. Several studies have provided a possible link between malnutrition and HRS development in patients with cirrhosis. A study by Plauth et al. found that malnutrition was a risk factor for HRS in patients with alcoholic cirrhosis [7]. Similarly, a study by Merli et al. reported an increased risk of HRS in patients with malnourished cirrhosis and ascites [8].

The prevalence of hepatorenal syndrome in patients with malnourished cirrhosis was also reported in other studies, who found that the prevalence of hepatorenal syndrome in malnourished cirrhosis patients was significantly higher (57%) than that in non-malnourished cirrhosis patients (36%). This study also reported a high mortality rate of 44% in patients with malnourished cirrhosis and HRS, highlighting the severity of this condition in this population. The mechanisms underlying the association between malnutrition and hepatorenal syndrome in patients with cirrhosis are not fully understood.

However, several potential explanations have been proposed, including a decrease in systemic vascular resistance, decrease in the production of nitric oxide (NO), a potent vasodilator, deficiency in various nutrients, such as vitamins and minerals, and electrolyte imbalance, which are essential for the proper functioning of the renal system[9]. However, these studies had small sample sizes, and could not explain the association between malnutrition and HRS because they did not specifically focus on malnutrition as a risk factor for HRS.

Therefore, this retrospective study investigated the prevalence of HRS in hospitalized malnourished liver cirrhosis patients and its association with nutrition-related factors. The findings of this study may help identify high-risk individuals and develop targeted interventions to prevent or delay the development of HRS in this population.

Materials and Methods

A retrospective chart review was conducted on patients with cirrhosis who were admitted to R L Jalappa Hospital between January 2017 and December 2022.

Patients who met the following prerequisites were included:

(1) diagnosis of cirrhosis based on clinical, laboratory, and imaging findings; and,

(2) malnutrition defined as a body mass index (BMI) <18.5 kg/m2 and serum albumin <3.5 g/dL, and

(3) Serum creatinine measurements during hospital stays.

Patients with acute kidney injury at admission or those on renal replacement therapy were excluded. Data were collected from medical records, including demographics, etiology of cirrhosis, severity of liver disease, body weight, body mass index, degree of malnutrition, ascites, and presence of HRS. The primary outcome was the prevalence of HRS in patients with cirrhosis and malnutrition, and the secondary outcomes included potential nutritional risk factors for developing HRS. Ascetic wet weight was subtracted before calculating the current body weight and BMI based on the available diagnostic report. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 23.0. Descriptive statistics, including mean and standard deviation (SD), were used to summarize the demographic characteristics of the patients, whereas frequency and percentages were used for categorical variables. Student's t- test, chi-square test, and correlation analysis were used to compare variables between the groups. P <0.05 considered statistically significant.

Results

Baseline characteristics of patients

A total of 385 cirrhosis patient records were included in the study. The mean age of the patients was 54 ± 19.20 years, with male predominance (96.88%), alcoholic etiology (98.18%) with average height of 165.45 cm, body weight of 67.03 kg with BMI of 24.39 kg/m2 MELD score of 12.69 ± 3.78, Child– Pugh class B or C indicating advanced liver disease, and serum albumin values of 3.21 gm/dL (Table 1). Most patients had a

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minimum of two complications, with portal hypertension being the highest, followed by GI bleed and ascites (95.32%, 43.89%, and 38.44% respectively. Patients had an average of 12 ± 7.3 days as the length of stay. All female patients were irregular to hospital and treatment; hence, they were excluded because of multiple missing data.

Indicators of malnutrition in HRS patients

Of these 385 patients, 93 (24.15%) developed HRS during their hospital stay associated with a BMI below 16.0 kg/m2, albumin < 2.8g/dL, creatinine >1.5 mg/dL, and severe ascites noted in 93.55% of the patients having a mean abdominal girth of 102 ± 11±06cm (P<0.05), indicating severe malnutrition (Table 2). The prevalence of HRS was significantly higher in severely malnourished cirrhosis patients than in adequately nourished cirrhosis patients with BMI >18.5 kg/m2 (76.34% vs. 4.30%, P<0.05). Majority of these patients (95.63%) had a minimum of five events of paracentesis before the diagnosis of HRS.

The majority of malnourished male cirrhosis patients with HRS were of type 1 (n=61) associated with lower body weights below 59.5 kg (average height of 165.45cm) with a BMI < 16.0 kg/m² and poor outcomes. The mean BMI in patients with HRS type 1 was significantly lower than that in patients without HRS (15.95 kg/m2 vs. 19.57 kg/m², p<0.05). Serum albumin levels were significantly lower in these patients with HRS type 1 (2.47 g/dL vs. 3.5 g/dL, p<0.05) and serum creatinine levels were higher (2.91 mg/dL vs. 0.59 mg/dL, p<0.05) compared to patients with mild malnutrition. (Table 3).

Furthermore, patients in the low BMI group experienced a notably greater incidence of complications related to HRS, such as spontaneous bacterial peritonitis (27% vs. 13%, p=0.02) and hepatic encephalopathy (31% vs. 18%, p=0.04). When comparing patients with a lower BMI to those who were only mildly malnourished, the overall mortality rate was higher (72% vs. 29.3%, p=0.01). In comparison to patients with BMI values that were close to normal, the mortality rate among patients with HRS was significantly higher in those with a lower BMI (73% vs. 31%, p=0.03). Low BMI was found to be a free predictor of death in patients with HRS on multivariate evaluation (OR 2.5, 95% CI 1.2-5.4, p=0.01).

Statistical significance

Low body mass index (OR=2.5, 95% CI: 1.5-4.1) and low serum albumin (OR=3.2, 95% CI: 1.8-6.0) were independent risk factors for the development of HRS in patients with chronic liver disease.

Discussion

With a prevalence of 24.15%, the study findings demonstrate that HRS is a frequent complication of cirrhosis. The findings of earlier research, which reported a prevalence ranging from 10% to 25%, are consistent with this finding[10,11]. In addition, our research supports the established correlation between the severity of liver disease and HRS[12].

The direct toxic effects of alcohol on the cause of higher kidneys are the prevalence of HRS in patients with alcoholic cirrhosis. Consistent with earlier research, patients with decompensated cirrhosis and higher MELD scores were also more likely to develop HRS. In line with earlier research, we also found that patients with malnourished liver cirrhosis had a high frequency of HRS[13]. Because of reduced liver function and increased systemic inflammation, malnutrition has been linked to an increased risk of developing HRS[14]. Our findings imply that malnutrition may be a major factor in the development of HRS in patients with liver cirrhosis.

According to earlier research indicating a higher prevalence of HRS in male patients, most HRS patients in our study were male[15, 16]. Alcohol misuse is more common among our HRS patients, which is the most common cause of liver cirrhosis. The substantial variation in serum albumin levels between patients with and without HRS emphasizes the importance of malnutrition in the onset of HRS. Due to reduced liver function and inadequate food intake, malnourished patients with liver cirrhosis have lower serum albumin levels, which causes hypoalbuminemia, a known risk factor for HRS [17].

This retrospective study found a high incidence of HRS in patients with malnourished cirrhosis by demonstrating a link between malnutrition and HRS onset in cirrhotic patients. Malnutrition can result in the loss of body weight and muscle mass, which in turn can affect the kidneys[18]. Malnutrition, which is associated with a higher risk of infection, can influence the onset of hepatorenal syndrome. The association between certain risk factors and the emergence of HRS, such as

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the degree of liver dysfunction and the presence of ascites, is supported by previous studies. Serum albumin, a protein that plays a crucial role in maintaining plasma volume and oncotic pressure, can be reduced during malnutrition. A low concentration of albumin in the blood can lead to a decrease in the effective circulation volume, which in turn can cause renal vasoconstriction and a decrease in the glomerular filtration rate. A decrease in the effective arterial blood volume is a key factor in the development of HRS[19].

Liver cirrhosis causes reduced nutrient intake, malabsorption, increased energy expenditure, and impaired hepatic protein synthesis. In patients with cirrhosis, malnutrition is associated with increased morbidity and mortality. The emergence of HRS in these patients further deteriorates their health. The majority of patients with HRS had type 1, which is associated with a worse prognosis than type 2[20]. Patients who had ascites with decreased appetite, inadequate food intake, loss of body weight, lower BMI range and severe ascites were more likely to develop HRS. On the other hand, patients with an alcoholic etiology had a higher risk compared to those with non-alcoholic cause because, alcohol is known to affect the nutritional status severely. A higher proportion of patients with HRS had a history of alcohol abuse and a Child-Pugh score of C, which was consistent with other studies.

Malnutrition is seen in cirrhosis patients with decreased appetite, limited food intake, and early satiety, which results in poor nutritional status. Although this association is not fully understood, it is likely a combination of factors that contribute to the development of HRS, such as changes in vascular resistance, nitric oxide production, gut microbiota, and micronutrient deficiency. Recognizing and treating malnutrition in patients with liver cirrhosis may avert the onset of HRS and enhance outcomes in this group.

Other essential nutrients required for the proper functioning of renal tubules can be decreased in cirrhosis patients with malnutrition. Several physiologically proposed mechanisms can explain the association between malnutrition and HRS. Insufficient nutrition results in decreased albumin production, which is essential for the regulation of plasma volume and systemic hemodynamics. A lack of nourishment can also decrease renal blood flow, which can further deteriorate renal function in patients with cirrhosis. The pathophysiology of HRS is influenced by renal vasoconstriction and decreased renal blood flow, resulting in acute kidney damage. The high prevalence of HRS in individuals with alcoholic liver disease and viral hepatitis is one of the few known pathologies.

The present study emphasizes the importance of early recognition and ongoing monitoring of kidney function, serum albumin, body mass index, and nutrient intake in patients with cirrhosis, particularly those at risk of malnutrition, and emphasizes the treatment of nutrient deficiencies in patients with cirrhosis. This study also emphasizes the necessity of periodic examination of muscle mass and nutrient status during routine follow-up visits for patients with liver disease. The introduction of dietary assistance is essential to prevent the progression of renal dysfunction and the emergence of HRS. Depending on the patient's condition, dietary support can take the form of an oral, enteral, or intravenous route.

The strengths of this study include a large sample size and the provision of assessing criteria for nutritional risk factors associated with HRS in patients with cirrhosis. This study also highlights the need for close monitoring of malnutrition and its timely management in patients with cirrhosis to prevent the development of HRS. However, there are some drawbacks to this investigation. Being a retrospective study, it is susceptible to selection bias and confounding factors. The findings may not be universally applicable to all liver disease sufferers, given the limitation of a single center of study participants.

Conclusion

HRS is a serious complication of liver disease and is more common in patients with inadequate nutrition. Malnutrition decreases the effective circulatory volume, electrolyte imbalances, and low serum albumin levels, all of which contribute to the emergence of HRS. Identifying and addressing HRS early is crucial for enhancing outcomes in this group. The outcomes of this study offer valuable insights into the association between malnutrition and HRS in patients with liver disease. It can also assist in identifying patients at risk and potentially direct medical professionals in implementing preventive measures to minimize the occurrence of HRS. Optimal nutritional support

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strategies for HRS management in malnourished cirrhosis patients require further exploration.

Abbreviations: HRS: Hepatorenal syndrome, DCLD: Decompensated chronic liver cirrhosis; MELD, model for end-, MELD: Model for End stage liver disease; CTP, Child–Turcotte–Pugh, CTP: Child Turcotte Pugh score

Conflict of Interest: None

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Tables :

Table:1 Baseline characteristics of the subjects

Variables	**Characteristics (males, n=385)**
Age (years)	54 (±19.20)
Gender, n (%) Male Female	 373 (96.88%) 12 (3.11%)
Etiology Alcohol Non-Alcohol	 378 (98.18%) 7 (1.81%)
Complications Portal HTN Hepatic encephalopathy Infections GI bleed Ascites	 367 (95.32%) 134 (34.80%) 113 (29.35%) 169 (43.89%) 148 (38.44%)
Disease severity MELD CTP	 12.69 (± 3.78) 7.94 (±1.16)
Body weight (kg)	67.03 (± 7.58)
Body mass index (kg/m²)	24.39 (± 1.74)
Serum albumin (g/dL)	3.21 (± 0.36)
Serum creatinine (mg/dL)	0.79 (± 0.2)
Abdominal girth (cm)	83.45 (± 9.21)
Length of stay (days)	12 ±7.3

Note: PHTN-portal hypertension, MELD- model for end stage liver disease, CTP- Child Pugh Turcotte score

Table 2: Characteristics and risk factors of patients with hepatorenal syndrome

Variables	**Patients without HRS (n=292)**	**With HRS (n=93)**	**P-value**
Body weight (Kg)	65.29 (±6.83)	59.51(±7.66)	0.0001

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Body mass index (kg/m²)			0.0001
Severely underweight (<16.0 kg/m²)	45 (15.41%)	71 (76.34%)	
Underweight (16 – 18.5 kg/m²)	109 (37.33%)	18 (19.35%)	
Normal (18.5 – 24.9 kg/m²)	121 (41.43%)	4 (4.30%)	
Overweight (>25 kg/m²)	17 (5.82%)	0	
Serum albumin (g/dL)			0.0011
>3.5 (g/dL)	9 (3.08%)	0	
2.8 – 3.5(g/dL)	203 (69.52%)	2 (2.15%)	
<2.8g/dL)	80 (27.39%)	91 (97.85%)	
Serum Creatinine (mg/dL)			0.0010
<1.2mg/dL)	257 (88.01%)	0	
1.2 -1.5 (mg/dL)	35 (11.98%)	0	
>1.5 (mg/dL) *	0	93 (100%)	
Ascites (grade)			0.0013
None	83 (28.42%)	0	
Mild – Moderate	149 (51.03%)	6 (6.45%)	
Severe	60 (20.55%)	87 (93.55%)	

**Note: Diagnostic criteria for HRS*
Nutrition-related risk factors for hepatorenal syndrome

Table 3: Nutritional associated factors for HRS in malnourished liver cirrhosis patients

Parameters	**Low risk**	**High risk**
Body weight (kg)*	>60 kg	< 52
BMI (kg/m²)	>18.5	<16.0
Albumin (g/dL)	>3.5	<2.8
Appetite	Good	Reduced significantly

*Note: *all subjects were male, mean weight was calculated for mean height of subjects with and without HRS at standard BMI of 22.5kg/m². Appetite was reduced in majority of patients with HRS and severity of diseases was progressive as documented in medical records.*